REMARKS

Applicants note with appreciation the detail and thoroughness of the examination embodied in Paper No. 20090128. This paper is submitted as fully responsive thereto.

Claims 1, 7, 29, 34-36, and 40 remain pending in the application.

Claims 1, 29, and 36 stand rejected under 35 U.S.C. §112, first paragraph, as failing to satisfy the enablement requirement.

Claims 1, 7, 29, 34-36, and 40 stand rejected under 35 U.S.C. §103(a) over Breitner (US 5,643,960) in view of Bustamante (JPET, 1997; 281:1381-1391) and Grilli (WO 98/20864).

Remarks directed to the rejection of claims 1, 29, and 36 under 35 U.S.C. §112, first paragraph, enablement.

Reconsideration and withdrawal of the rejections of claims 1, 29, and 36 as not being enabled by the specification for making and using solvates or hydrates of the claimed compounds is respectfully requested.

Paper No. 20090128 at page 4 identifies the only direction concerning solvates or hydrates at page 21. Applicants assert that the art recognizes more than just solvates or hydrates of a parent compound as prodrugs. Indeed, a prodrug is defined as one that is converted into a different form by a biologically relevant process. This is exemplified by the definition of prodrug in the subject specification at page 19, lines 16-18. Typically solvates and hydrates are forms of either a parent compound or a prodrug and do not create a prodrug from a parent compound. For example, esters of a particular compound will also serve as a prodrug. The subject specification provides several

examples of esters of CMT on page 19, lines 3-8 and indicates that typical methods of preparation are known in the art and applicable to CMT.

In addition, the specification provides ample guidance on pages 19-20 whereby two detailed publications illustrating how to make and use prodrugs are incorporated by reference for this purpose. The subject specification cites T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and "Bioreversible Carriers in Drug Design," ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987 for the considerations required to synthesize a prodrug of CMT. As such, a person of ordinary skill in the art has ample guidance as to how to make and use prodrugs of CMT.

Further, even if this guidance were not presented, the mere fact that making a compound requires experimentation does not render it non-enabled as long as the experimentation is not undue. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), aff'd. sub nom., *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Those of skill in the art routinely and regularly design modifications to drugs that are operable to be metabolized by the body. The vast number of pro-drugs available on the market serve as clear indicators that those of skill in the art routinely engage in such experimentation.

In view of the foregoing remarks, Applicants submit that a person of ordinary skill in the art has ample guidance concerning how to make and use a prodrug of CMT. Reconsideration and withdrawal of the rejections of claims 1, 29, and 36 under 35 U.S.C. §112, first paragraph, is respectfully requested.

Remarks directed to rejection of claims 1, 7, 29, 34-36, and 40 under 35 U.S.C. §103(a) over Breitner in veiw of Bustamante and Grilli.

Reconsideration and withdrawal of the rejections of claims 1, 7, 29, 34-36, and 40 under 35 U.S.C. §103(a) as unpatentable over Breitner in view of Bustamante and Grilli is respectfully requested as the cited prior art alone or in combination fails to provide any teaching of or reasonable expectation of success for the treatment of neurotrauma or inflammation associated with neuronal injury with choline magnesium trisalicylate (CMT).

The basis of the outstanding rejection is that Breitner teaches "a method of delaying the onset of Alzheimer's disease or related neurodegenerative disorders" with NSAIDs such as choline magnesium trisalicylate. (Paper No. 20090128, page 6.) (emphasis added, and omitted) The only motivations or reasonable expectation for success identified in the outstanding rejection is that other NSAIDs may be administered intrathecally or intracerebroventricularlly or to also administer deacetylated aspirin. *Id.* at 8.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Further, the prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). However, evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). Neither standard is met by the cited prior art combination.

First, no cited prior art teaches treatment of neurotrauma with CMT. Breitner is not cited as such, nor is there any suggestion therein for treatment with CMT. The entire underlying purpose of Breitner is to analyze past use of an NSAID and its correlation with subsequent onset of Alzheimer's

disease. Breitner does state, without being either enabling or sufficiently descriptive, that histamine H2 receptor blocking agents may be used therapeutically, but the only reference to NSAIDs is as a possibly co-administered agent. There is no suggestion that any NSAID is may be used as a treatment.

Second, a person of ordinary skill in the art has no reasonable expectation of success in modifying Breitner to administer CMT or any other NSAID for use as a therapeutic for the treatment of neurotrauma. The mechanisms of treatment and prevention are entirely unique. Breitner is not focused on any therapeutic benefit from the administration of any NSAID. No administration is taught therein. What Breitner associates is delayed onset of disease with past use. No data, chart, statement, or suggestion in Breitner indicates that the unique properties such as Ca^{2+} effects and remote secondary damage resulting from neurotrauma will be ameliorated by past or present administration of an NSAID. Further, animal experiments indicated that treatment of neurotrauma with an NSAID is ineffective. The subject specification teaches: Up to now, drugs have been used that are only marginally effective in preventing this cascade of events and non-steroidal inflammatory drugs (NSAIDS) have not been useful in animal models for neurotrauma." (page 8, lines 11-14.) The specification teaches that this may be due to inhibition of platelet function, a process which is not differentiated by Breitner. Indeed, Breitner while preferring COX-2 selective compounds, teaches that selectivity is not necessary. Further, Breitner teach that aspirin "alone appeared to produce weak but similar effect to NSAIDs." (col. 8, lines 54-55.) It is clear that aspirin will not be effective for the treatment of neurotrauma at least because it will increase bleeding – a wholly undesirable side effect following trauma. This leads a person of ordinary skill in the art to the conclusion that the mechanisms of prevention are entirely different form the mechanisms of treatment.

The lack of any reasonable expectation of success flows directly from the data of Breitner itself. No suggestion as to any ameliorative effect of any NSAID treatment was identified in Breitner. In each case, those treated with NSAIDs who had Alzheimer's disease were diagnosed with the same disease state as those who received no treatment. As such, a person of ordinary skill in the art reads Breitner as suggesting that there is no therapeutic benefit to administration of any NSAID, if one had actually been administered after disease onset.

The cited purposes of Bustamante as teaching alternate delivery modes of compounds other than CMT, or the teaching of Grilli of deacetylated aspirin fail to bolster the deficiencies of Breitner.

In view of the above remarks, reconsideration and the withdrawal of the rejections of claims 1, 7, 29, 34-36, and 40 under 35 U.S.C. §103(a) over Breitner in view of Bustamante and Grilli is solicited.

Summary

Claims 1, 7, 29, 34-36, and 40 are the claims pending in this application. Each claim is believed to be in proper form and directed to allowable and patentable subject matter. Reconsideration and allowance of the claims is requested. Should the Examiner find to the contrary, she is respectfully requested to contact the undersigned attorney in charge of this application to resolve any remaining issues.

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Respectfully submitted,

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